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Early detection of changes in the feet of diabetic patients with indicator test Neuropad®

A disturbed sweat secretion at the foot due to autonomic diabetic neuropathy is easy to diagnose.

O. Schnell¹, M. Müller², E. Standl¹



O. Schnell

Introduction

The diabetic foot syndrome is one of the commonest and most severe complications of diabetes mellitus. Despite numerous efforts, such as the St. Vincent Declaration (1), there has been no reduction in the number of amputations of the lower limbs of diabetic patients. Because diabetes mellitus is frequently accompanied by diabetic polyneuropathy, loss of pain sensation means that there is often a delay in recognising foot ulcers and infections, and these conditions may even be overlooked altogether. Treating foot injuries that have arisen in this way is complex and expensive, not least because of common concomitant diseases associated with diabetes, such as peripheral occlusive arterial disease. Regular foot examinations and identification of patients at high risk of developing diabetic foot syndrome have assumed great importance in the prevention of diabetic foot complications.

The German Health Report Diabetes 2008, drawn up by the German Diabetes Union and the National Action Forum Diabetes Mellitus, recommends that patients should have their feet examined every three, six or twelve months, depending on their risk profile (2). There are indications that diabetic foot syndrome is still being given too little attention in clinical practice. Examinations of the feet are often carried out in practice only on a minority of patients and only on about 50 % of patients hospitalised for a lengthy period (3–5).

Summary

The diabetic foot syndrome is one of the most frequent and most severe diabetic complications. Foot ulcers are associated with high costs for health care and a significantly reduced quality of life, and often go undetected by diabetic patients. They also frequently lead to the need for amputation. Preventing the development of foot ulcers is, therefore, of crucial importance. This can best be done through the early identification of patients at risk. Regular and thorough foot examinations are, however, a comparatively lengthy and tedious procedure. The indicator test Neuropad® is an easy-to-use, simple screening test, which is applied to the foot and, through colour coding, enables the quick assessment of the sudomotor function and the extent of peripheral neuropathy. It can easily be used by the patients themselves. This indicator

test enables the reliable identification of patients at high risk for the diabetic foot syndrome.

Key words

diabetic foot syndrome, colour coding indicator pad Neuropad®, screening test, prevention

Diabetische Fußveränderungen früh erkennen mit Farbindikatorpflaster Neuropad®

Zusammenfassung

Das komplexe Krankheitsbild des diabetischen Fußsyndroms stellt eine der häufigsten und schwersten Komplikationen des Diabetes dar. Ulzerationen, die aufgrund der diabetischen Neuropathie oftmals vom Patienten nicht bemerkt werden, führen Jahr für Jahr nicht nur zu hohen Behandlungskosten, sondern auch beim Patienten zu massiven Einschränkungen der Lebensqualität. Häufig sind Amputationen die Folge. Die Prävention der Entstehung von Fußulzerationen, indem Risikopatienten frühzeitig identifiziert werden, hat somit eine hohe Priorität. Die regelmäßige und vollständige Untersuchung der Füße von Diabetikern ist in der Praxis jedoch vergleichsweise aufwendig. Mit dem Indikatorpflaster Neuropad®, das am Fuß

aufgebracht wird und durch Farbumschlag in wenigen Minuten eine Aussage über die Funktion der Schweißdrüsen und damit den Stand der peripheren Neuropathie zulässt, steht nun ein einfacher, auch von Patienten selbst nutzbarer Screeningtest zur Verfügung, der nach bisherigen Untersuchungen die zuverlässige Identifikation von Hochrisikopatienten für das diabetische Fußsyndrom ermöglicht.

Schlüsselwörter

diabetisches Fußsyndrom, Farbindikatorpflaster Neuropad®, Screeningtest, Prävention

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Since regular examinations of the feet of diabetic patients also play a key preventive role, a diagnostic test method that can quickly and reliably identify patients at risk would be desirable.

Neuropad® provides a new diagnostic method for the early detection of changes in diabetic patients' feet. The

New data published by the AOK, Germany's biggest health insurance company, even suggests a markedly higher number of amputations than had previously been assumed (24).

The diabetic foot – a multifactorial disease

The diabetic foot syndrome is not easy to define since it is a complex clinical picture (32–38). It develops as a result of the interplay of several different factors which give rise to different clinical conditions of varying degrees of severity. The most important cause of the development of diabetic foot syndrome is diabetic neuropathy: the development of sensory neuropathy leads to a loss of sensation in the region of the foot. Injuries and traumas are incorrectly perceived or not perceived at all, promoting the development of foot ulcers (39). Motor neuropathy leads to a flexion deformity of the toes and thus to an abnormal manner of walking. This leads to the development of atypical compressive loads, e.g. under the heads of the metatarsal bones, which can lead to lesions. Autonomous neuropathy gives rise to excessively dry skin with cracks and fissures. It also causes increased blood flow, which leads to a warm foot, swollen by oedemas.

Arteriovenous (AV) shunts in the subcutis, which lead to increased blood circulation in this region, are opened, whereas capillary perfusion of the overlying dermis is restricted. This adversely affects the sweat glands, hair follicles and sebaceous glands located in that area, leading to dry, cracked and fissured skin (32–39).

Autonomous neuropathy also leads to reduced flexibility in the joints. This also results in an altered gait pattern, which also causes untypical compressive loads and shear stress on the foot. The untypical load leads to repeated traumas, which are not perceived and which for their part lead to untypical and increased hard skin formation (calluses). These calloused parts of the skin lead for their part to lesions again. Consequently, subkeratotic haematomas develop not infrequently under a callus and ulcers develop on the exposed areas.

Peripheral occlusive arterial disease (POAD) is the second important risk factor for the development of ulcers and diabetic foot syndrome. Since POAD and neuropathy often coexist, oedemas and septic thrombosis, which can occlude end arteries, thereby causing gangrene in the foot, are often only discovered at a later stage, because of the patient's impaired sensory perception. Occlusive microangiopathy is unlikely to be a cause of an

A diagnostic test method that can quickly and reliably identify patients at risk of developing diabetic foot syndrome would be desirable.

aim of this review is to summarise previously published studies and to demonstrate the value of Neuropad® in diagnosing diabetic foot syndrome.

Epidemiology of the diabetic foot

Diabetic patients develop foot gangrene approximately 20 to 50 times more frequently than non-diabetic patients (6–17). About 14 % of German diabetic patients require medical treatment every year because of foot problems (18, 19).

The diabetic foot syndrome exacts a high toll: currently, about 240 000 patients suffer from foot lesions in Germany, about 120 000 diabetic patients develop a new lesion each year and about 25 000 diabetic patients have to undergo amputations because of diabetic foot syndrome (12, 14, 20, 21).

About 70 % of all amputations in Germany are carried out on diabetic patients, especially on elderly patients (cf. Fig. 1). Most of these amputations are above-the-ankle amputations (major amputations) which are associated with a high mortality rate (22–25). The incidence of amputations in Germany is thus comparatively high compared with other European countries (15, 26–29). While there has been a reduction in the number of amputations in recent years in some European countries, a similar reduction has not yet taken place in Germany, as is borne out by several studies (15, 29–31).

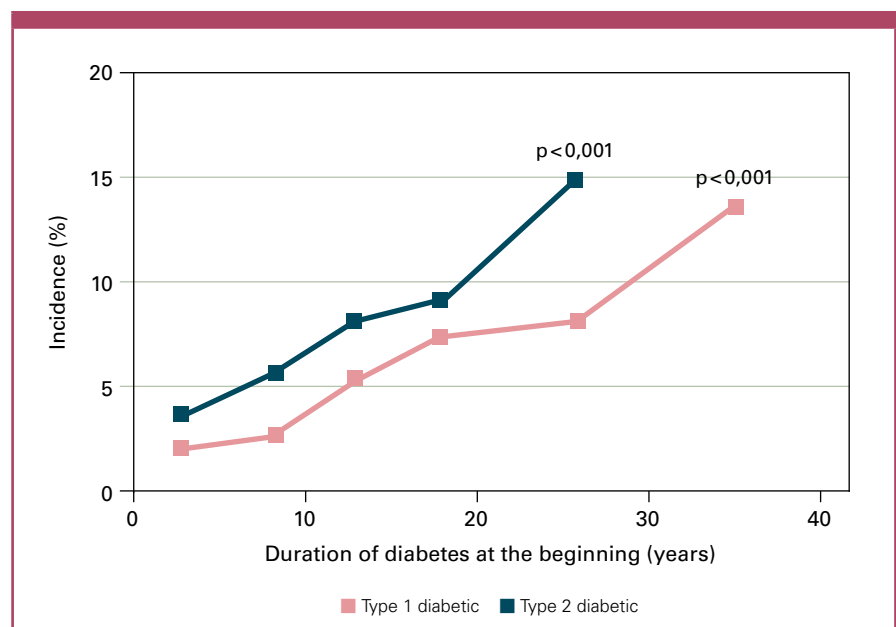


Fig. 1: Cumulative 10 year incidence of amputations of the lower extremities related to duration of diabetes at the start in type 1 and type 2 diabetes (44).

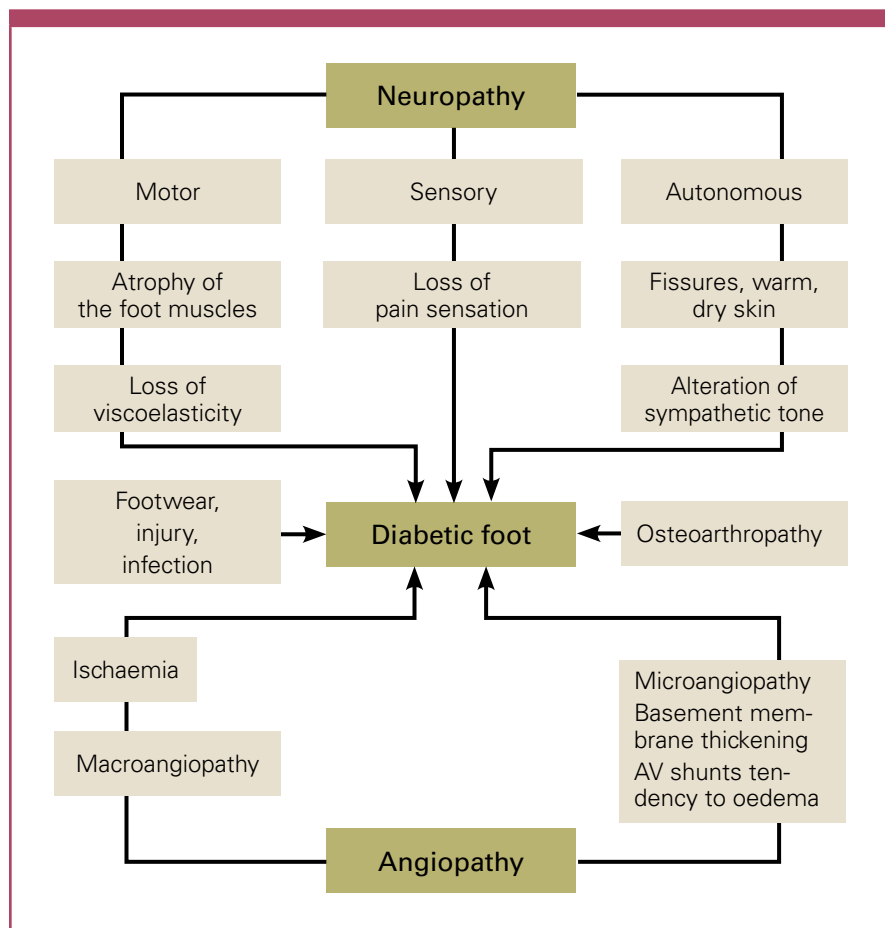


Fig. 2: Pathogenesis of diabetic foot ulcerations (39).

ulcer, according to the latest research findings (40, 41). However, functional microangiopathy can be detected (41). Apart from the endogenous risk factors referred to above, external causes can also contribute to the development of foot ulcers in diabetic patients. These external factors include foot deformities caused by pre-existing ulcers or operative procedures, poor quality footwear, acute mechanical loads and also thermal and – infrequently – chemical traumas. These are factors of which the patients are not aware, possibly because of their impaired sensory perception. The interplay of several or all the named factors leads to diabetic foot syndrome (cf. Fig. 2). In order to prevent its development, high-risk patients must be identified at as early a stage as possible.

High long-term costs

The diabetic foot syndrome costs the health care system vast amounts of

money, primarily due to the long periods of hospitalisation, the protracted periods of rehabilitation and the subsequent cost of home care and other social services. The cost of an amputation due to diabetic foot syndrome is particularly high because high costs continue to accrue for rehabilitation after the amputation. These make up up to 77% of the total costs (42).

Although the cost of treatment of diabetic foot syndrome (cf. Fig. 3) sometimes varies in the literature, which is primarily due to the services and periods of time recorded, the cost of diabetic foot syndrome represents in every case a severe financial burden on the health care system.

In the USA, the cost of foot ulcers due to neuropathy is approximately 10.7 billion US dollars a year, corresponding to 27% of the costs due to diabetes or 9% of the total expenditure in the American health care system (43). The cost of diabetic foot syndrome in Germany is around 1.8 billion

Euros and rising (44). The recurrence rates in diabetic foot ulcers are also responsible for the continuously high and rising costs. Prospective studies demonstrate a high rate of recurrences. In this connection, Apelqvist and his co-workers describe a recurrence rate of 34% after one year, 60% after three years and 70% after five years (45).

Importance of Prevention

The high recurrence rate in the case of diabetic foot syndrome of up to 70% (44), an amputation rate of 12%, survival rates of only 58% compared with 79% of a comparable section of the healthy population (45) and the high cost of treatment clearly show that preventive foot care makes a great deal of sense (46–48). Apart from secondary and tertiary prevention, primary prevention is thus of great importance, since this can reduce the prevalence of diabetic foot syndrome by 50% (49).

The most important measure here is regular inspection and examination of the feet with the aim of identifying high risk patients. The American Diabetes Association (ADA) recommends annual foot examinations, which should also include the condition of the skin of the feet and should be combined with at least two neurological examination procedures (50). Since a regular examina-

Primary prevention can reduce the prevalence of a diabetic foot syndrome by 50%.

tion of the feet of diabetic patients, as can be seen from the literature (3, 4), does not routinely take place, presumably because of the relatively high costs involved, there is a need for a reliable and simple screening test that reliably identifies patients at risk and can ideally also be carried out by patients themselves. Neuropad®, which has recently become available, provides such a diagnostic test and its study results compared with conventional diagnosis are now examined.

How Neuropad® works

Apart from POAD, diabetic polyneuropathy is the principal cause of the development of a diabetic foot. With increasing nervous dysfunction, the function of the sweat glands on the feet also diminishes and can completely cease. As a result, the skin of the foot becomes brittle and dry, making it more susceptible to lesions and thus to ulcers. This is where diagnosis using the Neuropad® plaster comes in. Neuropad® examines the function of the sweat glands by means of a colour indicator.

This colour indicator, a cobalt-II-salt, is applied in the form of a plaster to the area of skin on the patient's foot to be examined. In healthy patients, the moisture (sweat) on the foot changes the colour of the Neuropad® plaster from blue to pink normally within a few minutes. However, if the colour does not change completely or only very slowly, this indicates initial nerve damage. This test is, as yet, the only one that can document changes in the moistness of the foot. The speed and scale of the colour change of the Neuropad® plaster can thus be assessed as indicators of

In some of the patients, an abnormality in sweat secretion was detected with no symptoms of neuropathy.

sudomotor function and thus as indicators of diabetic neuropathy as well. Fig. 4 gives an overview of the use of the Neuropad® and possible test results. The purpose of Neuropad® is to identify patients at risk of developing diabetic foot syndrome at an early stage in order to prevent or delay the onset of diabetic foot syndrome. Its ease of application as a plaster is also designed to enable patients to use the plaster themselves.

Review of studies

Early patient awareness

In recent years, different studies have been published about the use of

Author	Country	Costs in USD
<i>Primary Healing</i>		
Bouter et al. (1988)	The Netherlands ^a	10 000
Apelqvist et al. (1994)	Sweden ^c	7 000
<i>Healing with Amputation</i>		
Connor (1987)	Great Britain ^a	14 000
Bouter et al. (1988)	The Netherlands ^a	15 000
Bild et al. (1989)	USA ^a	8 000–12 000
Reiber (1992)	USA ^b	20 000–25 000
Thompson et al. (1993)	New Zealand ^a	11 000
Apelqvist et al. (1994)	Sweden ^c	43 000 ^d –65 000 ^e
van Houtum et al. (1995)	The Netherlands ^a	14 500
<i>Long Term Costs (3 year period)</i>		
Apelqvist et al. (1995)	Sweden ^c	<i>Primary Healing</i> 16 100 ^f –26 700 ^g <i>Healing with Amputation</i> 43 100 ^d –63 100 ^e

^a) Hospital costs, ^b) inclusive rehabilitation, ^c) absolute direct costs until healing, ^d) minor amputation, ^e) major amputation, ^f) without ischaemia, ^g) with ischaemia

Fig. 3: Cost of diabetic foot syndrome associated with ulcers and non-traumatic lower extremity amputations (guideline from the German Diabetes Association (DDG)).

Neuropad® on diabetic patients. Zick and his colleagues published a study in 2003 in which 40 diabetic patients, some of whom were known to have peripheral neuropathy, and 27 healthy control persons were examined using Neuropad® in order to determine the extent of the sweat secretion on the sole of the foot (51). The indicator plaster changed colour within 10 minutes among nearly all the people in the control group, whereas with the diabetic patients there was a clear delay before the colour changed or there was no change in colour at all. In the examination of the diabetic patients, it also became apparent that a section of the patients examined displayed an abnormality in sweat secretion, although the patients still did not display any symptoms of neuropathy. Zick concluded from this that autonomous neuropathy preceded sensory neuropathy, a finding that his previous studies also appeared to confirm (52). The authors therefore considered Neuropad® to be particularly suitable for identifying diabetic patients who have an increased risk of developing diabetic foot syndrome at an early stage by means of the indicator test. The researchers were also of the opinion that the test was highly suitable for securing

full cooperation from the patients. Since Neuropad®, like a diabetic test strip, presents its test results visually in an easy-to-understand way, patients develop trust in the method and pay more attention to their feet which are at risk, even if they already suffer from sensory nervous disturbances in the foot. This provides an additional means of promoting the early detection and prevention of foot ulcers.

Evaluation of the test

Papanas and his working group published a study in 2004 which evaluated the effectiveness of Neuropad® in diagnosing peripheral neuropathy in type 2 diabetic patients (53). They examined 104 type 2 diabetic patients with regard to polyneuropathy, using the Diabetic Neuropathy Index (DNI). Impairment of the sudomotor was additionally assessed using the Neuropad® method. The results of the working group demonstrated the high degree of sensitivity of the Neuropad® method: peripheral neuropathy was clinically diagnosed in 71 patients (68.3%) using DNI. Changes to the sweat gland secretion was established in 67 of these patients (94.4%),

using Neuropad®. It was also confirmed that a reduction in sweat gland secretion not infrequently also exists in patients displaying no symptoms of peripheral neuropathy. The sensitivity of the Neuropad® test was 94.4 % and its specificity was 69.7 % compared with the DNI. The study also showed that the time elapsing before the Neuropad® plaster changed colour was directly related to the extent of nerve damage. The results suggested to the authors that Neuropad®'s high degree of sensitivity made it very well suited for diagnosing peripheral neuropathy, since a change could be detected in the sudomotor even of diabetic patients who had not yet developed any clinical symptoms of neuropathy.

At the “6th Scientific Meeting of the Diabetic Foot Study Group 2006”, Manes and colleagues presented a multicentre study in which the indicator test was evaluated on 506 diabetic patients. They concluded that the indicator test is suitable as a screening tool for identifying diabetic patients with a high risk of developing diabetic foot syndrome (54). Shen and colleagues evaluated the indicator test on an Asian population and came to the same conclusion (55).

Reproducibility of the test

Papanas and his team also examined the reproducibility of the Neuropad® test results (56). This involved examining

142 type 2 diabetic patients on two different days with Neuropad®. The test results were almost identical at 98 % (cf. Fig. 5). In the same study, the reproducibility of the test results was also tested by different examiners. Here, too, there was an almost complete concordance of results.

All in all, Neuropad® thus produced an excellent reproducibility of test results, irrespective of the examiner – unlike conventional diagnosis.

Comparison with other investigation procedures

Several research groups carried out comparisons between the Neuropad® test and other examination procedures. Papanas and his colleagues published a study in connection with this in 2007 (57). The Neuropad® indicator plaster and clinical examination methods, especially the determination of the vibratory threshold, were used and compared in diagnosing diabetic polyneuropathy among 156 type 2 diabetic patients. Neuropathy was diagnosed in 90 (58.4 %) of the patients examined. 88 (97.8 %) of the patients with neuropathy and 21 (32.8 %) of patients without neuropathy had an impairment of the sudomotor ($p < 0.001$). Both the Neuropad® test and the determination of the vibratory threshold showed a high degree of sensitivity during diagnosis, which marks out Neuropad® as an additional diagnostic

tool, which the authors consider to be particularly suitable for screening tests or for use by the patients themselves, because of its ease of application.

A study from Turkey was also published in 2007 (58), in which the test results of Neuropad® were compared with the corrected QT time (QTc), a method of diagnosing autonomous neuropathy. Sensitivity, specificity, as well as positive and negative predictive value

The time elapsing before the plaster changes colour is directly related to the extent of nerve damage.

were examined. Neuropad® once again showed a high degree of sensitivity and a high negative predictive value, although it was not superior to the QTc measurement.

In a study from Greece (59), special attention was given to the usefulness of Neuropad® in diagnosing cardiac autonomic neuropathy and peripheral sensorimotor neuropathy. The study showed that Neuropad® has a high sensitivity and a negative predictive value for diagnosing peripheral sensorimotor neuropathy, whereas the test showed low sensitivity for diagnosing cardiac autonomic neuropathy.

In a further study from the same year, Papanas and his working group compared the sensitivity and specificity of Neuropad® with the nerve conduction velocity (NCS: Nerve Conduction Study). Here too Neuropad® at 95.2 % showed a high degree of sensitivity for diagnosing clinical neuropathy, which at 94 % exceeded even the NCS. While the specificity of Neuropad® in diagnosing clinical neuropathy was only moderately high at 62.1 %, it was by contrast very high at 96 % in detecting neurophysiological neuropathy (abnormal NCS). All in all, it was again shown that the Neuropad® test not only has a high degree of sensitivity in diagnosing diabetic neuropathy, but is also valid when compared with other methods, such as NCS. Moreover, Papanas and his colleagues once again demonstrated in their study that the time elapsing until

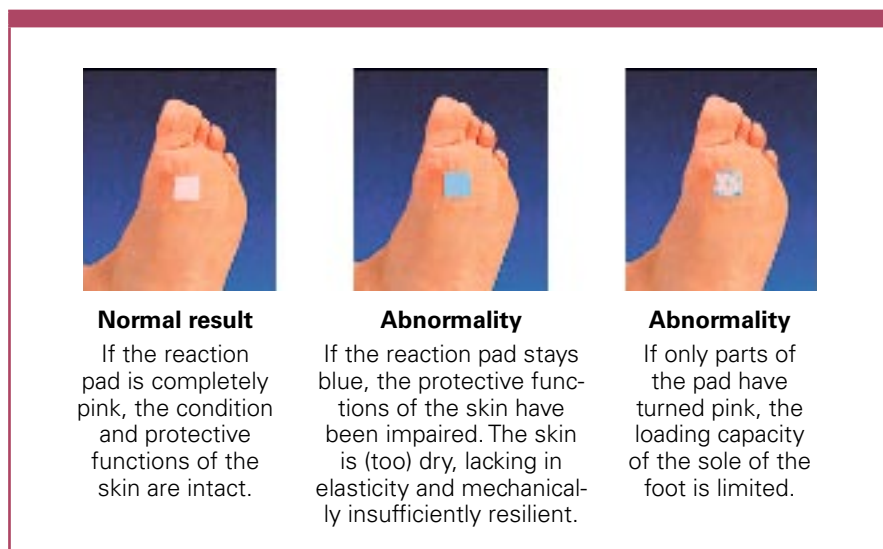


Fig. 4: How Neuropad® works.

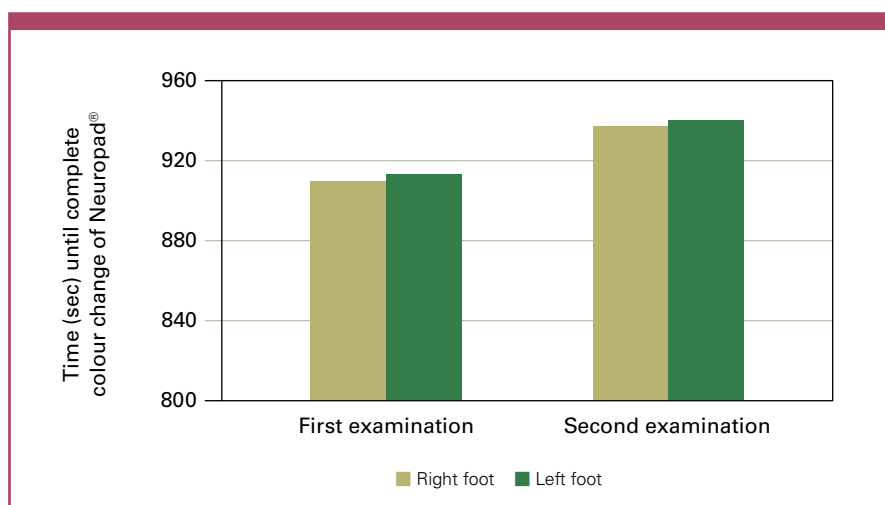


Fig. 5: Time until complete colour change of indicator test on right and left foot at two different examination times. Each examination showed a highly significant correlation ($r=0.001$, $p=0.001$) of both feet.

the colour change was directly related to the extent of the pre-existing nerve damage (60).

The colour indicator test correlates with the cold detection threshold on the foot and with the heart rate on forced respiration.

Self-testing by the patient

Tentolouris demonstrated that Neuropad® was also highly suitable for self-application by patients (61). He examined with his colleagues 152 patients with type 2 diabetes with regard to neuropathy, with the results of the clinical-neurological examination by the physician being compared with the Neuropad® home diagnosis made by the patients. The patient had been instructed in advance how to use the plaster and been given the plaster to take home with them to carry out a self-test. In the assessment of the indicator test (normal–abnormal) there was a high degree of concordance at 90.3 % between the results of the patients and physicians. The sensitivity of the indicator plaster for diagnosing neuropathy established was 87 % and the specificity 68.9 %, values which confirm earlier studies (53).

A new study shows that, in the case of diabetic patients, the Neuropad® colour

indicator test also correlates with the Neuropathy Disability Score (DSS), the cold detection threshold on the foot and the heart rate on forced respiration (Quattrini). The intraepidermal density of nerve fibres, which was examined in this study by a skin biopsy in the area of the foot, has also been associated with the results of Neuropad® (62). Fig. 6 shows the intraepidermal density of nerve fibres in both control subjects and diabetic patients with a normal and pathological colour indicator test (62).

Summary

Neuropad® is a colour indicator test in the form of a plaster which, by

changing colour, provides information about the function of the sweat glands and thus about neuropathic changes affecting the foot. The extensive studies carried out to date show that a positive Neuropad® test indicates changes associated with a high risk of developing diabetic foot syndrome. Neuropad® also enables incipient changes in sweat gland secretion to be detected without using complicated methods. In all currently available studies, Neuropad® displayed a very high degree of sensitivity for detecting peripheral neuropathy. The test results correlate well with the presence of peripheral sensorimotor neuropathy and to a lesser degree with indications of cardiac autonomic neuropathy. While the specificity of Neuropad® was lower in most of the studies, it was nevertheless comparable with the values of established methods.

Neuropad® thus enables patients at risk of developing diabetic foot syndrome to be identified at a very early stage by means of screening tests so that they can be closely monitored and given preventive therapy. The high level of reproducibility of the test results was demonstrated in several studies. Moreover, several studies demonstrated that the speed and completeness of the colour change of the indicator plaster correlate with the extent of nerve damage and also with the polyneuropathy classification systems. This serves to emphasise the validity of the method. The simplicity of the Neuropad® test means that patients can carry it out themselves,

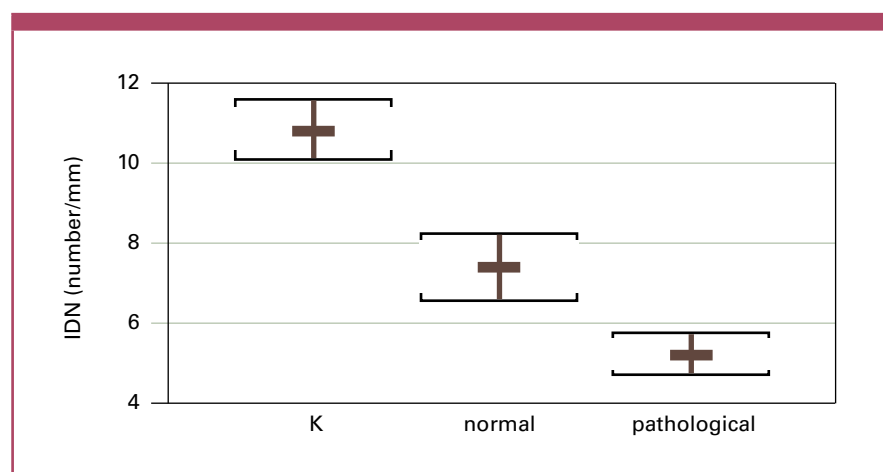


Fig. 6: The intraepidermal density of nerve fibres (IDN) is significantly ($p=0.02$) lower for diabetics with pathological neuropad test compared to diabetics with normal neuropad result; K shows a normal result of a healthy control person (62).

enabling them to be actively involved in the therapy process, if required.

The studies conducted show that, in comparison with established procedures such as 10-g monofilament, the pin prick test and the tuning fork test, Neuropad® delivers objective and reproducible results and, at the same time, is not dependent on the cooperation of the patient. Furthermore, the consumption of Neuropad® plasters could also serve in future as a record of how many diabetic patients undergo prophylactic foot examinations (per year, for example). This would also make Neuropad® a useful tool in the framework of disease management programmes (DMPs).

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